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## The "Ocular Glymphatic System"

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## The “Ocular Glymphatic System”: An Important Missing Piece in the Puzzle of Optic Disc Edema in Astronauts?

We read with great interest the article by Mathieu et al.<sup>1</sup> entitled “Evidence for Cerebrospinal Fluid Entry Into the Optic Nerve via a Glymphatic Pathway,” recently published in *Investigative Ophthalmology & Visual Science*. The authors provided the first evidence of cerebrospinal fluid (CSF) entry via paravascular spaces into the orbital optic nerve in mice and concluded that this pathway may be highly relevant to optic nerve diseases, including glaucoma.<sup>1</sup> We fully agree with this notion, and we believe that the “ocular glymphatic system” may also play a key role in the development of optic disc edema in astronauts.

Ophthalmic abnormalities including optic disc edema, globe flattening, choroidal and retinal folds, hyperopic refractive error shifts, and nerve fiber layer infarcts have been reported in astronauts returning from long-duration space flight on the International Space Station.<sup>2</sup> Understanding factors contributing to this space flight-associated neuro-ocular syndrome (SANS) is one of the top priorities for the National Aeronautics and Space Administration (NASA), especially in view of future long-duration interplanetary space flight missions, including trips to Mars. Currently, the exact mechanisms causing SANS are unknown. These ophthalmic findings after long-duration space flight were initially referred to as the visual impairment and intracranial pressure (VIIP) syndrome,<sup>2</sup> and a leading hypothesis is that VIIP is caused by elevated intracranial pressure (ICP) resulting from microgravity-induced cephalad fluid shifts leading to venous stasis in the head and neck.<sup>3,4</sup> This stasis could cause impairment of CSF drainage into the venous system and cerebral venous congestion, both of which could lead to a rise in ICP.<sup>4</sup> The resulting elevated ICP could lead to optic nerve sheath distention, globe flattening, and stasis of axoplasmic flow with optic disc swelling.<sup>4</sup> We believe that the existence of an ocular glymphatic system offers an attractive additional explanation for how microgravity may cause optic disc edema in astronauts.

Evidence from the recent study by Mathieu et al.<sup>1</sup> is supportive of the hypothesis that a paravascular transport system exists within the optic nerve, analogous and likely continuous with the recently discovered glymphatic system in the brain. The authors reported the entry of CSF into the optic nerve via spaces surrounding blood vessels, bordered by astrocytic endfeet.<sup>1</sup> Intriguingly, new research also indicates that the ocular glymphatic system may provide an anatomical basis for posterior fluid outflow from the eye. Indeed, in a PhD thesis defense, Xiaowei Wang<sup>5</sup> demonstrated the existence of an ocular glymphatic pathway by intravitreal injection of fluorescently conjugated human amyloid- $\beta$  and subsequent confocal and stereofluorescent imaging examination of the retina as well as the optic nerve of the injected eye. The trans-lamina cribrosa pressure difference (TLCPD), that is, the difference of intraocular pressure (IOP) minus ICP, was identified as the major driving force for the glymphatic ocular outflow to the optic nerve.<sup>5</sup> Normally, IOP exceeds ICP, and on average there is a small force (mean 4 mm Hg) directed posteriorly across the lamina cribrosa.<sup>6</sup>

We hypothesize that a glymphatic flow imbalance mechanism at the optic nerve head may, at least partially, explain the development of optic disc swelling in astronauts during long-duration space flight. Although Mathieu et al.<sup>1</sup> did not observe entry of CSF tracers into the optic nerve head, in the case of

microgravity-induced intracranial hypertension, CSF may be forced under high pressure into the subarachnoid space (SAS) of the optic nerve, enter the nerve through the paravascular spaces surrounding the central retinal vessels, and from there infiltrate the intraocular space through the surroundings of the retinal vascular system. This may resemble, to some extent, the situation of sudden intracranial hypertension in patients with Terson syndrome. Terson syndrome is an intraocular hemorrhage arising secondary to intracranial hemorrhage.<sup>7</sup> The pathway of subarachnoid hemorrhaged blood into the eye in Terson syndrome is still controversial. On the basis of magnetic resonance imaging findings of Terson syndrome and their review of the literature, Sakamoto et al.<sup>7</sup> speculated that there may be a continuous network of paravascular channels that surround the central retinal vessels in the optic nerve and their branches in the retina, and that they may serve as drainage channels from the SAS around the optic nerve to beneath the internal limiting membrane. In the setting of microgravity-induced intracranial hypertension, raised ICP may similarly facilitate paravascular CSF influx into the eye. As noted above, the posteriorly directed TLCPD may ensure effective glymphatic outflow from the eye.<sup>5</sup> However, in astronauts, reduction or reversal of the normal TLCPD, due to increased ICP, may result in a one-way valve-like mechanism between the glymphatics in the retina and optic nerve, leading respectively to a partial or complete obstruction of the posterior fluid outflow from the eye. This may result in glymphatic stasis, predominantly within the prelaminar region of the optic nerve head, and we believe that this could contribute to the optic disc edema observed in astronauts. The accumulation of toxic metabolites due to glymphatic stasis then may cause further disc swelling. Additionally, the same concept could offer a better understanding of the pathogenesis of papilledema in patients with terrestrial idiopathic intracranial hypertension (IIH). Evidence to support this view was recently presented by Denniston et al.<sup>8</sup> who reported the potential relevance of the ocular glymphatic system to IIH.

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